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Citation for published version:

Mazein, A, Watterson, S, Gibbs, H, Hsieh, W, Ba Abdullah, M, Blanc, M, Griffiths, WJ, Freeman, T & Ghazal, P 2011 'Regulation and feedback of cholesterol metabolism' Nature Publishing Group.
<https://doi.org/10.1038/npre.2011.6315.1>

Digital Object Identifier (DOI):

[10.1038/npre.2011.6315.1](https://doi.org/10.1038/npre.2011.6315.1)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Early version, also known as pre-print

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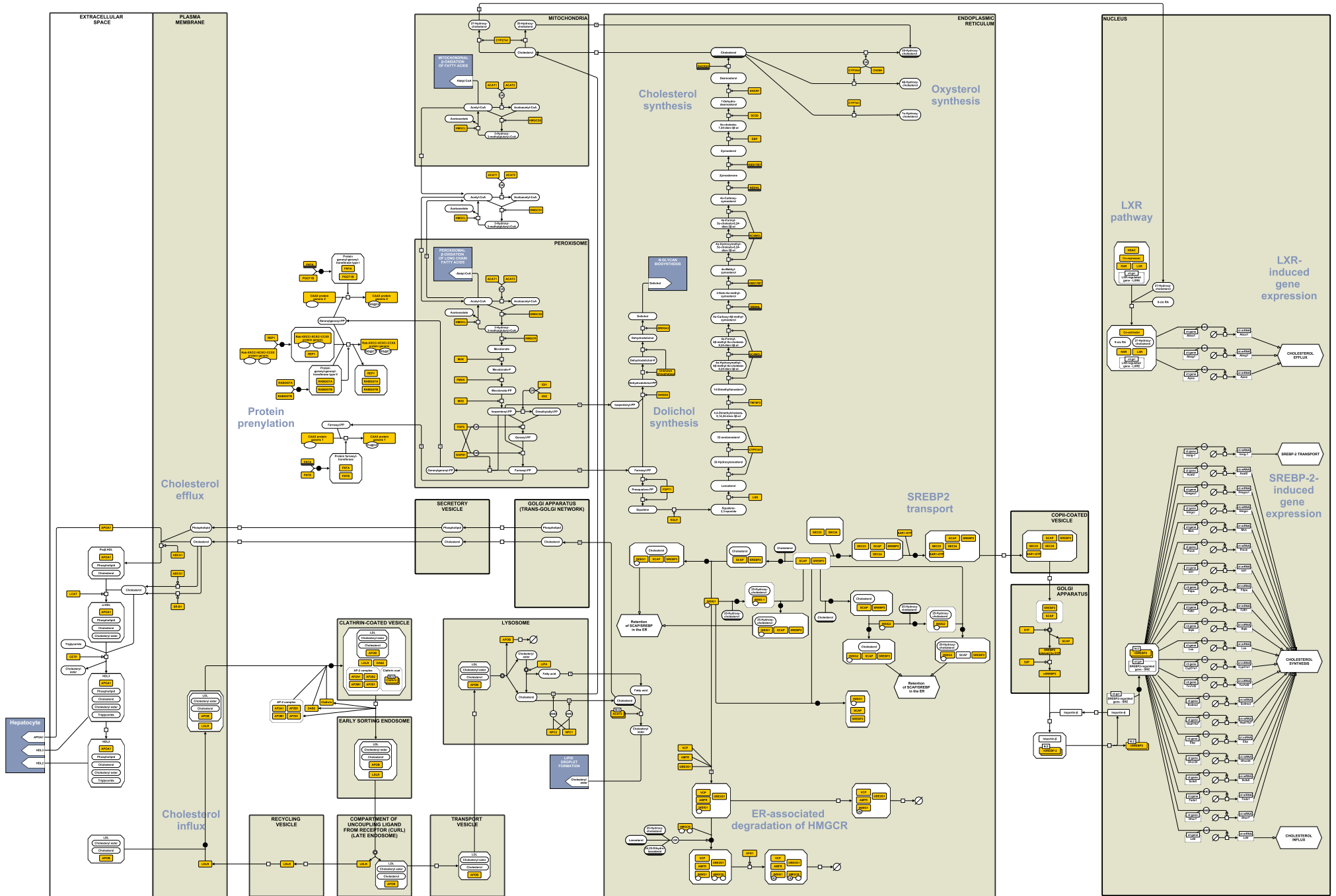


Regulation and Feedback of Cholesterol Metabolism

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Cholesterol biosynthesis serves as a central metabolic hub for numerous biological processes in health and disease. An integrative knowledge representation of how the cholesterol pathway is structured and how it interacts with other pathway systems is lacking. Here we provide using Systems Biology Graphical Notation the research synthesis of a process diagram integrating the regulatory and feedback systems for cholesterol synthesis.

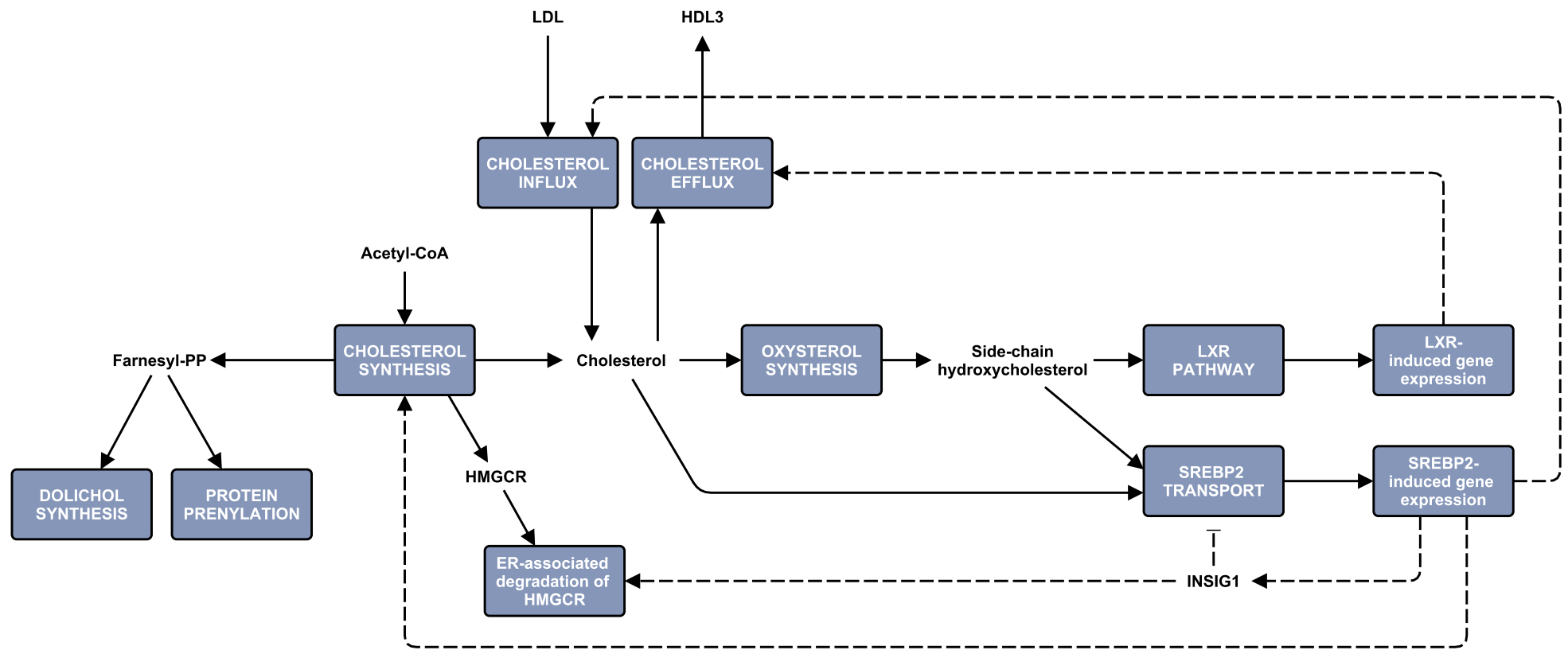
Cholesterol is an intensively studied, multi-functional lipid that is key to many aspects of immunological, neuronal, viral and hepatocyte biology. It is an essential component of cellular membranes and is a precursor to steroids, bile acids and vitamin D whilst its own precursors contribute to prenylation and dolichylation. As a consequence of its broad role, tightly regulated mechanisms have evolved to ensure intracellular homeostasis of the cholesterol biosynthesis pathway.

Despite the importance of the sterol biosynthesis pathway to cellular function and its value in pharmaceutical therapies, an integrative picture of how the pathway is structured and how it interacts with other pathway systems has not been well described in the literature.

Here, we present a pathway diagram that provides an integrative consensus view of the current level of understanding of the sterol biosynthesis pathway, its relationship with other pathways of note and its associated feedback mechanisms. This model of the sterol biosynthesis pathway has been assembled using a variety of publicly available resources including the research findings of the LipidMaps consortium (<http://www.lipidmaps.org>) and results obtained from thorough searches of the published literature that have been manually curated and validated by domain experts. It is most relevant to macrophage biology.

The model that we present here is described using the Systems Biology Graphical Notation¹ (SBGN), a community driven consensus graphical schema for capturing the molecular details of pathway systems, although many other schema exist that can be used to provide alternative descriptions, such as mEPN². The Systems Biology Graphical Notation Process Description language Level 1 scheme³ was used in a slightly modified form. We used a different shape for simple chemicals in order for compound names to fit within. The pathway names such as “cholesterol synthesis” or “SREBP transport” are also not a part of SBGN PD language and are used on the scheme for the readers' benefit.

Together with the SBGN model, we include a simplified schematic that shows the relationship between the pathway subsystems that are related to cholesterol biosynthesis.



The model can be broadly described as a system that combines: cholesterol influx, cholesterol efflux, protein prenylation, dolychol synthesis, cholesterol synthesis, ER associated degradation of HMGCR, SREBP2 transport, oxysterol synthesis, the LXR pathway, SREBP2-induced gene expression and LXR-induced gene expression.

We also include a list of the published literature from which the model has been assembled and a list of UniProt Ids for the proteins captured in the model.

This is a multi-scale model that captures the details of absorption and efflux of cholesterol between the cell and the blood plasma. However, it is not completely exhaustive. The LDL and VLDL transport systems are not captured. It describes the cholesterol processing that occurs in each organelle of the cell and the transcriptional control that mediates feedback to ensure cholesterol homeostasis.

Cholesterol biosynthesis itself constitutes a sequence of metabolic transitions that occur across several organelles, starting with the processing of acetyl-CoA in the mitochondria. This pathway branches into the protein prenylation arm, which has been shown to be critical to optimal CMV infection⁴, and the sterol arm that is responsible for cholesterol production. Feedback occurs through SREBP2 transport. The SCAP:SREBP2 complex, which ordinarily is chaperoned to the nucleus to activate the suite of enzymes associated with the cholesterol biosynthesis pathway, is instead retained in the endoplasmic reticulum, in the presence of relatively high concentrations of intracellular cholesterol or side-chain hydroxylated cholesterol, in particular 25-hydroxycholesterol. This acts to down-regulate transcription of the enzymes acting on the sterol biosynthesis pathway until ordinary levels of cholesterol and its derivatives have been reached.

It has been reported that SCAP:SREBP2 is significantly retained when cholesterol concentration exceeds 5% of total endoplasmic reticulum lipids⁵. However, it would appear that the sensitivity of the feedback mechanism to sterol levels is dependent on expression as overexpression of Insig-1 has been shown to lower this threshold to 3%⁵.

INSIG1 is transcriptionally dependent on SREBP2, while INSIG2 is not⁶. When intracellular cholesterol rises, we would expect SREBP2 retention to lead to a fall in de novo INSIG1 synthesis. As the free and unbound INSIG1 protein declines, this would lead to INSIG2 becoming dominant in the process of SREBP2 retention. Differences between the affinity of INSIG1 and INSIG2 for complex formation will emerge at this point as a change to the feedback sensitivity. As cholesterol levels start to fall, retained SREBP2 will be increasingly transported to the nucleus, boosting INSIG1 synthesis and restoring the pool of INSIG1 protein available to respond to further fluctuations in cholesterol levels.

This regulation impacts not just upon cholesterol, but also upon the oxysterols downstream of cholesterol and upon the LXR genes, downstream of the oxysterols. In the diagram presented, the transcriptional output of the genes affected has not been directly connected to the corresponding enzymes in the cholesterol biosynthesis pathway for the benefit of clarity.

We hope that by elucidating and integrating the details of this pathway and its context, this will form the basis of a finer level of understanding of the pathway and its function and that this will add a greater insight to future studies of the sterol biosynthesis pathway.

¹Le Novere *et al.* *Nature Biotechnology* **27**, 735 - 741 (2009).

²Freeman *et al.* *BMC Systems Biology* **4**, 65 (2010).

³Moodie *et al.* *Nature Precedings* <http://dx.doi.org/10.1038/npre.2011.3721.4> (2011).

⁴Blanc *et al.* PLoS Biology **9**(3), e1000598 (2011).

⁵Radhakrishnan *et al.* Cell Metabolism **8**, 512 – 521 (2008).

⁶Yabe et al. Proceedings of the National Academy of Sciences USA **100**(6), 3155-3160 (2003).

Acknowledgements

CSBE is a Centre for Integrative Systems Biology funded by BBSRC and EPSRC award D019621. This work was supported by Wellcome Trust program grant WT066784 (to PG).

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UniProt References

| PROTEIN NAME | UNIPROT ID | SYNONYMS | COMMENTS |
|------------------------|------------|----------|----------|
| ABCA1 | O95477 | | |
| ABCG1 | P45844 | | |
| ACAT1 | P35610 | SOAT1 | |
| ACAT2 | O75908 | SOAT2 | |
| AMFR | Q9UKV5 | | |
| AP2A1 | O95782 | | |
| AP2B1 | P63010 | | |
| AP2M1 | Q96CW1 | | |
| AP2S1 | P53680 | | |
| APOA1 | P02647 | | |
| APOB | P04114 | | |
| CAAX PROTEIN GENERIC 1 | NA | | GENERIC |
| CAAX PROTEIN GENERIC 2 | NA | | GENERIC |
| CETP | P11597 | | |
| CH25H | O95992 | | |
| CLATHRIN | NA | | GENERIC |
| CYP27A1 | Q02318 | | |
| CYP3A4 | P08684 | | |
| CYP51A1 | Q16850 | | |
| CYP7A1 | P22680 | | |
| DAB2 | P98082 | | |
| DHCR24 | Q15392 | | |
| DHCR7 | Q9UBM7 | | |
| EBP | Q15125 | | |
| FDFT1 | P37268 | | |
| FDPS | P14324 | | |
| FNTA | P49354 | | |
| FNTB | P49356 | | |
| GGPS1 | O95749 | | |
| HDAC | NA | | GENERIC |
| HMGCL | P35914 | | |
| HMGCR | P04035 | | |
| HMGCS1 | Q01581 | | |
| HMGCS2 | P54868 | | |
| HSD17B7 | P56937 | | |
| IDI1 | Q13907 | | |
| IDI2 | Q9BXS1 | | |
| INSIG1 | O15503 | | |
| INSIG2 | Q9Y5U4 | | |
| LCAT | P04180 | | |

| PROTEIN NAME | UNIPROT ID | SYNONYMS | COMMENTS |
|---|------------|----------|----------|
| LDLR | P01130 | | |
| LIPA | P38571 | | |
| LSS | P48449 | | |
| LXR | NA | | GENERIC |
| LXRA | Q13133 | NR1H3 | |
| LXRB | P55055 | NR1H2 | |
| MVD | P53602 | | |
| MVK | Q03426 | | |
| NPC1 | O15118 | | |
| NPC2 | P61916 | | |
| NSDHL | Q15738 | | |
| PGGT1B | P53609 | | |
| PMVK | Q15126 | | |
| RABGGTA | Q92696 | | |
| RABGGTB | P53611 | | |
| RAB-XXCC/-XCXC/-CCXX PROTEIN GENERIC | NA | | GENERIC |
| REP1 | P24386 | | |
| RXR | NA | | GENERIC |
| RXRA | P19793 | | |
| RXRB | P28702 | | |
| RXRG | P48443 | | |
| S1P | Q14703 | MBTPS1 | |
| S2P | O43462 | MBTPS2 | |
| SAR1-GTP | Q9NR31 | | |
| SC4MOL | Q15800 | | |
| SC5D | O75845 | | |
| SCAP | Q12770 | | |
| SEC23 | NA | | GENERIC |
| SEC24 | NA | | GENERIC |
| SQLE | Q14534 | | |
| SR-B1 | Q8WTV0 | | |
| SREBP2 | Q12772 | | |
| TM7SF2 | O76062 | | |
| UBE2G1 | P62253 | | |
| UFD1 | Q92890 | UFD1L | |